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Culture-negative sepsis may be a different entity from culture-positive sepsis: a prospective nationwide multicenter cohort study

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Abstract

Background The distinction between culture-positive sepsis and culture-negative sepsis regarding clinical characteristics and outcomes remains contentious. We aimed to elucidate these differences using large-scale nationwide data.

Methods This prospective cohort study analyzed data from the Korean Sepsis Alliance registry, comprising 21 intensive care units (ICUs) across 20 hospitals from September 2019 to December 2021. Patients meeting the Sepsis-3 criteria were included.

Results Among 11,981 sepsis patients, 3501 were analyzed, all of whom were referred to the ICU through the emergency department (mean age: 72 ± 13 years; 1976 [56%] males). Of these, 2213 (63%) were culture-positive sepsis and 1288 (37%) were culture-negative sepsis. Compared to the culture-positive sepsis group, the culture-negative sepsis group exhibited less severe illness, with lower Sequential Organ Failure Assessment scores and less deteriorated vital signs. While pulmonary-origin sepsis was common in both groups, culture-negative patients primarily presented with pulmonary infections and had a higher incidence of respiratory failure. In comparison to the culture-positive sepsis group, blood cultures and the administration of empirical antibiotics were performed less promptly in the culture-negative sepsis group. Patients with culture-negative sepsis also showed lower compliance with fluid resuscitation (98.4% vs. 96.9%, p = 0.038; culture-positive sepsis vs. culture-negative sepsis) and received vasopressors earlier (31.1% vs. 35.9%, p = 0.012). In-hospital mortality did not differ significantly between the two groups (31.6% vs. 34.9%, p = 0.073); however, in patients with septic shock, culture-negative sepsis had higher mortality rates (37.6% vs. 45.1%, p = 0.029). The apparent appropriateness of empirical antibiotics in the culture-negative septic shock was higher than that of the culture-positive septic shock (85.2% vs. 96.8%, p < 0.001). Culture-negativity independently predicted poor prognosis in septic shock patients (OR: 1.462, 95% CI [1.060–2.017], p = 0.021).

Conclusion In patients with septic shock, culture-negativity was associated with increased mortality, despite the paradoxically higher appropriateness of empirical antibiotics than culture-positive patients. These contradictory findings suggest that the current criteria for determining the appropriateness of empirical antibiotic therapy may not be valid for culture-negative sepsis.

Keywords Sepsis, Shock, septic, Culture, Negative result, Treatment outcome

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Introduction

Background

The debate over culture-positive sepsis versus culture-negative sepsis revolves around whether they are distinct diseases with unique clinical profiles and prognoses. In managing patients with culture-negative sepsis, clinicians often resort to empirical antibiotics derived from microbiological data of culture-positive sepsis cases with similar infections, raising concerns about appropriateness. Unlike culture-positive sepsis, where pathogen identification and antibiotic susceptibility testing guide targeted antibiotic adjustments, culture-negative sepsis management lacks such certainty, posing challenges particularly in severe cases of sepsis. Even when these patients improve, uncertainties persist regarding the safety of de-escalating antibiotics given the lack of bacterial identification and its antibiotics susceptibility.

Previous studies have yielded mixed findings depending on the type of sepsis studied. In a study of adult sepsis patients diagnosed with the Sepsis-2 definition, no significant mortality differences were observed between the culture-positive sepsis and culture-negative sepsis groups [1]. In research on patients with severe sepsis, outcomes have been inconsistent. One study found that culture-negative patients experienced lower hospital mortality rates and less organ dysfunction than culture-positive patients [2]. However, a large-scale study using the National Inpatient Sample database showed contrary results to these findings [3]. When confined to septic shock, two retrospective cohort studies showed no disparity in mortality and severity between culture-negative septic shock and culture-positive septic shock patients [4, 5]. Whereas, a single-center study reported similar mortality and less organ dysfunction in patients with culture-negative septic shock compared with and culture-positive septic shock [6]. Recent meta-analyses highlighted the need for a study involving a larger number of patients [7, 8].

Objectives

The aim of our study was to determine whether culture-negative patients represent a distinct group compared with culture-positive patients in a large-scale sepsis cohort based on the Sepsis-3 definition. Our hypothesis was culture-negative sepsis is a different entity from culture-positive sepsis in terms of clinical profiles and prognosis.

Methods

Study design and setting

This study is a retrospective analysis of a prospective cohort data from an ongoing nationwide registry of the Korean Sepsis Alliance (KSA), which enrolled patients from 21 intensive care units (ICUs) across 20 participating hospitals between September 2019 and December 2021. The detailed protocols for patient enrollment and data collection have been previously described [9].

This study was approved by the institutional review boards (IRBs) of each participating hospital, including the Inje University Sanggye Paik Hospital Institutional Review Board (IRB No. 2018-08-014-013). Informed consent for each patient was waived due to the non-interventional and observational nature of the study.

Participants

Eligible patients for the KSA registry were 19 years of age or older and assessed for sepsis according to the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) [10] in the emergency department or general ward. The inclusion criteria are detailed in the Supplementary Materials. This study focused on patients referred to the ICUs through the emergency department.

Sepsis was defined as a probable or confirmed diagnosis of infection accompanied by an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 or more points associated with the infection. Septic shock was identified by the need for vasopressors to maintain a mean arterial pressure of 65 mmHg or higher, along with a serum lactate level exceeding 2 mmol/L in the absence of hypovolemia [10].

Culture-positive sepsis was defined as sepsis with the isolation of a bacterial pathogen based solely on ordinary bacterial cultures from blood or relevant infectious foci within 48 h after time zero. It excluded the microbiological results based on polymerase chain reaction (PCR) test, antigen test, serology and toxin assay. A positive culture decision was made only when the isolated strain met the criteria for semi-quantitative testing for each infectious foci (Supplementary Materials).

Culture-negative sepsis was defined as a case in which microbial infection was suspected but the causative microorganism of sepsis has not been identified in any microbial test including bacterial culture. These tests included ordinary bacterial culture, acid-fast bacilli (AFB) smear/culture, PCR test, antigen test, serology and toxin assay for the specimens obtained from suspected infection sites such as blood, urine, sputum (or endotracheal aspirates when available), bronchoalveolar lavage fluid, bile, cerebrospinal fluid, or biopsy tissue.

Variables

The primary outcome was in-hospital mortality. Detailed hospital outcomes were also investigated. First, we divided the patients into whether they died or survived in hospital and then, if they survived and were discharged from the hospital, we checked whether they were

discharged home or to another institution. In this case, it was confirmed whether the patient went to a step-down facility or a step-up facility.

"Time zero" was defined as the time of triage upon arrival at the emergency department [11].

The appropriateness of empirical antibiotic therapy was determined by whether the isolated causative organisms were susceptible to the empirical antibiotics in culture-positive patients. Whereas, in culture-negative patients, it was assessed based on whether the empirical antibiotics administered were recommended in the relevant guidelines (Supplementary Materials). In both patient groups, the administration of empirical antibiotics was considered appropriate only if it started within 24 h from time zero.

Adjunctive corticosteroid treatment was defined as the use of steroids to treat hemodynamic instability.

Source control is defined as surgical or non-surgical intervention to treat sepsis.

Data sources

Data were prospectively collected by research coordinators at each center using an electronic case report form (http://sepsis.crf.kr/) [12]. The data were regularly monitored by a data management team, and each center underwent periodic audits by the steering committee. All consecutive patients were followed until death or hospital discharge. Collected information included demographic data such as age, sex, and comorbidities, underlying general conditions such as clinical frailty score, Eastern Cooperative Oncology Group (ECOG) performance status, and Charlson comorbidity index as well as severity score such as the SOFA score. Additionally, physiologic and laboratory variables including inflammatory markers such as C-reactive protein (CRP) and procalcitonin, source and type of infection, and the presence of multidrug-resistant (MDR) pathogens in culture-positive patients were recorded. Detailed information on the sepsis workup is provided in the Microbiologic evaluation section in the Supplementary Materials. Treatment data encompassed initial fluid therapy, adjunctive steroid therapy, appropriateness of empirical antibiotic therapy and daily use of ICU resources and medical events during ICU stay. Outcome data included in-hospital mortality and ICU mortality rates and the post-discharge destination for survivors.

Study size estimation

Unlike the previous studies [1–4, 6, 13], our study employed a more recent definition of sepsis (Sepsis-3). Based on one of the previous studies [1] with the most similar patient group, the sample size was estimated at 2360 patients with a Type I error probability of 0.05 and a Type II error risk of 0.8.

Statistical methods

Statistical analyses were conducted using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as medians (interquartile range [IQR], 25–75%) or means ± standard deviation (SD), and categorical variables are reported as frequencies (percentages). Data were compared using the Student's *t*-test for parametric values and the Mann–Whitney U test for nonparametric values. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. After univariate analyses, variables with p-values <0.05 were included in stepwise backward multivariate logistic regression analyses. All analyses considered a two-tailed p-value of <0.05 as statistically significant.

To handle missing data, we utilized the 'mice' package in R. By default, the 'mice' package employs the predictive mean matching (pmm) algorithm for continuous variables and logistic regression (logreg) for categorical variables to impute missing values. Both pmm and logreg impute missing values by matching the missing data with observed data from other variables. The 'mice' package also creates multiple imputed datasets for modeling, and the final imputed dataset is generated by averaging these datasets. The default setting uses five imputed datasets.

Data access and cleaning methods

Patients were excluded from analysis if their infection was caused by non-bacterial pathogens, including viruses, fungi, or M. tuberculosis, or if their causative bacteria were identified by methods other than culture, such as PCR, antigen tests, serologic tests, or toxin assays. For all other patients, researchers at each institution judged sepsis into culture-positive sepsis or culture-negative sepsis as defined above. Subsequently, patients enrolled in the general wards or referred to the non-ICU units were also excluded.

Results

Participants

A total of 11,981 patients were diagnosed with sepsis during the study period (Fig. 1). After the exclusion of 8,480 patients for reasons detailed in the Methods, 3,501 patients with community-onset sepsis referred to the ICU through the emergency department were included.

Clinical characteristics of culture-positive *sepsis* and culture-negative *sepsis* groups

The mean age was 72 ± 13 years, and 1976 (56%) were males. Their baseline SOFA scores was 6.4 ± 3.1. Of these patients, 2213(63%) were diagnosed with culture-positive

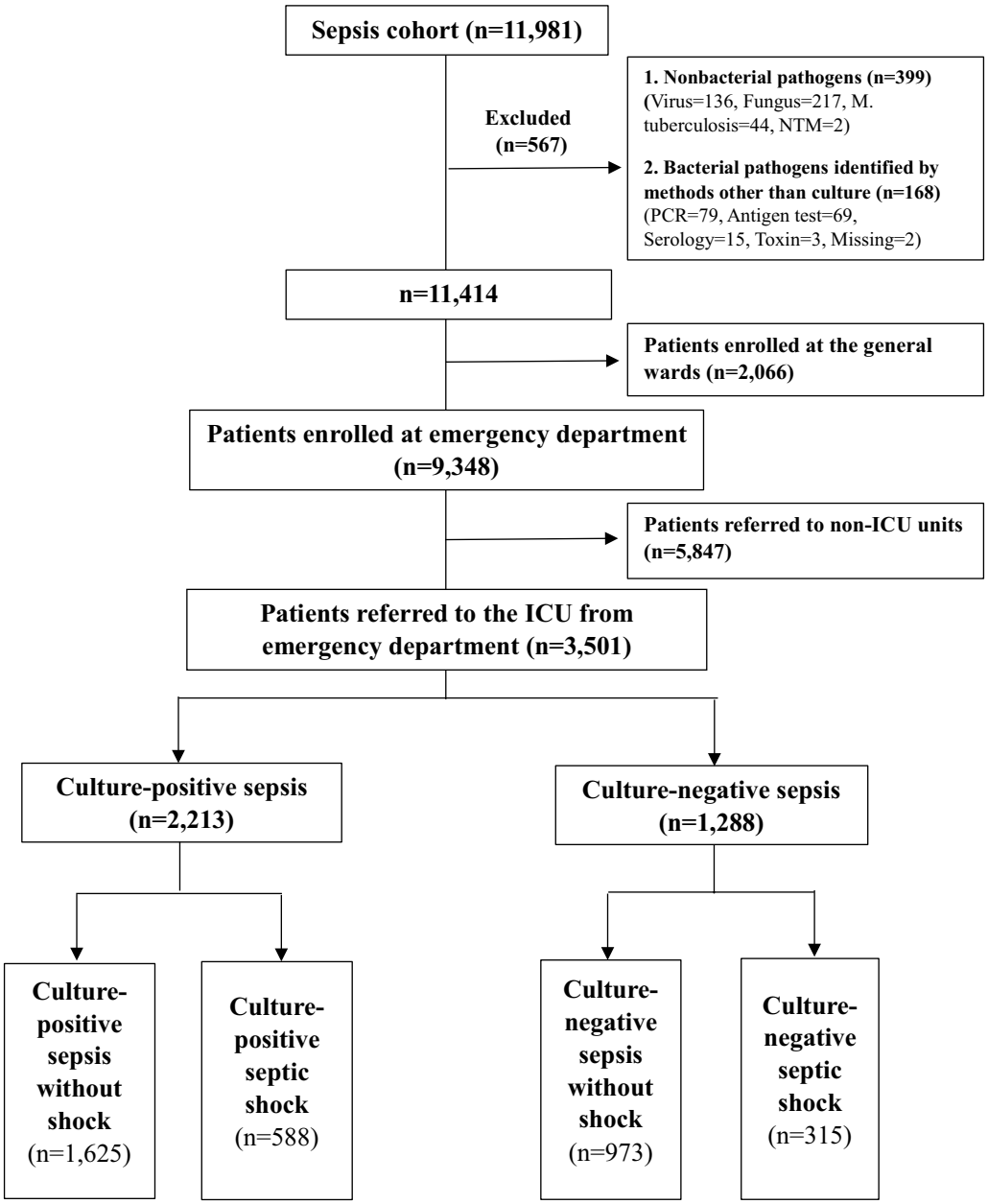
Sepsis cohort (n=11,981)
Excluded (n=567)
1. Nonbacterial pathogens (n=399) (Virus=136, Fungus=217, M. tuberculosis=44, NTM=2)
2. Bacterial pathogens identified by methods other than culture (n=168) (PCR=79, Antigen test=69, Serology=15, Toxin=3, Missing=2)
n=11,414
Patients enrolled at the general wards (n=2,066)
Patients enrolled at emergency department (n=9,348)
Patients referred to non-ICU units (n=5,847)
Patients referred to the ICU from emergency department (n=3,501)
Culture-positive sepsis (n=2,213)
Culture-negative sepsis (n=1,288)
Culture-positive sepsis without shock (n=1,625)
Culture-positive septic shock (n=588)
Culture-negative sepsis without shock (n=973)
Culture-negative septic shock (n=315)

Fig. 1 Flow chart

sepsis, while 1288 (37%) were diagnosed with culture-negative sepsis.

Differences in demographic characteristics between the two groups are summarized in Table 1. The culture-negative sepsis group was younger and presented with less severe illness, as indicated by lower SOFA scores, compared to the culture-positive sepsis group. A closer examination of the SOFA score components revealed that the culture-positive sepsis group had higher scores for coagulopathy and hepatic failure, while the culture-negative sepsis group had a higher PaO_2/FiO_2 (P/F) ratio score. Although pulmonary origin was the most common in both groups, it was more frequent in the culture-negative sepsis group. In contrast, urinary tract infections (UTIs) were significantly more frequent in the culture-positive sepsis group. Upon arrival at the emergency department, the culture-positive sepsis group exhibited lower mean blood pressure and higher body temperature compared to the culture-negative sepsis group. Laboratory results showed that the culture-positive sepsis group had a

Table 1 Baseline and clinical characteristics of patients with culture-positive and culture-negative sepsis referred to the ICU (n = 3501)

Characteristics	Total (n = 3501)	Culture-positive sepsis (n = 2213)	Culture-negative sepsis (n = 1288)	Missing* (%) (n = 3501)
Age, yrs	72 ± 13	73 ± 13	71 ± 13	0
	75 [64–81]	75 [65–82]	73 [63–81]	
Sex, male, n (%)	1976 (56)	1224 (55)	752 (58)	0
Body mass index, kg/m^2	22.0 ± 4.4	22.0 ± 4.4	21.9 ± 4.5	87 (2.4)
	21.6[18.9–24.5]	21.7[19.0–24.6]	21.5[18.8–24.5]	
Baseline SOFA score	7.2 ± 3.1	7.3 ± 3.1	7.0 ± 3.1	0
	7 [5–9]	7 [5–9]	7 [5–9]	
SOFA_PaO_2/FiO_2 ratio	1.64 ± 1.08	1.57 ± 1.08	1.75 ± 1.07	0
	2 [1, 2]	1 [1, 2]	2 [1, 2]	
SOFA_PLT	0.85 ± 1.13	0.94 ± 1.16	0.69 ± 1.05	1
	0 [0–2]	0 [0–2]	0 [0–1]	
SOFA_Bilirubin	0.59 ± 0.93	0.67 ± 0.98	0.46 ± 0.82	4
	0 [0–1]	0 [0–1]	0 [0–1]	
SOFA_CV	1.25 ± 1.30	1.26 ± 1.27	1.25 ± 1.35	0
	1 [0–1]	1 [0–1]	1 [0–1]	
SOFA_GCS	1.51 ± 1.36	1.49 ± 1.34	1.55 ± 1.40	0
	1 [0–3]	1 [0–3]	1 [0–3]	
SOFA_Renal	1.32 ± 1.126	1.35 ± 1.25	1.27 ± 1.28	3
	1 [0–2]	1 [0–2]	1 [0–2]	
Clinical frailty score	5.4 ± 2.1	5.5 ± 2.0	5.2 ± 2.1	0
	6[4-7]	6 [4-7]	5 [4-7]	
ECOG performance status	2.3 ± 1.3	2.3 ± 1.3	2.1 ± 1.3	0
	2 [1-3]	3 [1-3]	2 [1-3]	
Charlson comorbidity index	5.4 ± 2.5	5.5 ± 2.5	5.2 ± 2.5	0
	5 [4-7]	5 [4-7]	5 [4-7]	
Comorbidities				
Diabetes mellitus	1352 (39)	880 (40)	1472 (37)	0
Solid tumor malignancy	886 (25)	561 (25)	325 (25)	0
Hematologic malignancy	120 (3)	74 (3)	46 (4)	0
Chronic neurologic disease	974 (28)	646 (29)	328 (26)	0
Cardiovascular disease	897 (26)	579 (26)	318 (25)	0
Chronic lung disease	482 (14)	262 (12)	220 (17)	0
Chronic kidney disease	532 (12)	333 (15)	199 (16)	0
Chronic liver disease	325 (9)	212 (10)	113 (9)	0
Immunocompromised	74 (2)	54 (2)	20 (2)	
Type of infection				
Community-acquired	2350 (67)	1451 (66)	899 (70)	0
Hospital-acquired	266 (8)	209 (10)	57 (4)	0
Nursing hospital acquired	534 (15)	357 (16)	177 (14)	0
Nursing home-acquired	351 (10)	196 (9)	155 (12)	0
Type of sepsis				
Sepsis	2598 (74)	1625 (73)	973 (76)	0
Septic shock	903 (26)	588 (27)	315 (25)	0
Source of sepsis				
Lung	1606 (46)	866 (39)	740 (58)	0
Intraabdominal	840 (24)	553 (25)	287 (22)	0
Urinary tract	653 (19)	556 (25)	97 (8)	0
Systemic infection without 1° site	254 (7)	136 (6)	118 (9)	0
Skin or soft tissue	110 (3)	79 (4)	31 (2)	0

Table 1 (continued)

Characteristics	Total (n = 3501)	Culture-positive sepsis (n = 2213)	Culture-negative sepsis (n = 1288)	Missing* (%) (n = 3501)
Nervous system	25 (0.7)	11 (0.5)	14 (1.1)	0
Catheter-related	13 (0.4)	12 (0.5)	1 (0.1)	0
Hemodynamics				
Mean arterial blood pressure, mmHg	67 [56–80]	67 [56–78]	67 [56–84]	36 (1.0)
Heart rate, beats/min	105 [88–122]	105 [88–121]	105 [87–122]	17 (0.5)
Respiratory rate, breaths/min	24 [20–26]	23 [20–26]	24 [20–28]	24 (0.7)
Body temperature, °C	37.0[36.3–38.0]	37.2[36.4–38.2]	36.8[36.2–37.8]	9 (0.3)
Baseline laboratory findings				
WBC, 10^3/μL	11.8 [7.1–17.4]	11.8 [6.7–17.5]	11.9 [7.7–17.2]	0
Neutrophil, %	86.9[78.5–91.7]	88.4[80.3–92.4]	84.0[75.9–90.0]	28 (0.8)
Hematocrit	32.9[28.0–38.2]	32.8[27.9–37.7]	33.1[28.2–39.0]	0
Platelet,10^3/L	164 [97–248]	153 [89–232]	186 [115–270]	0
Albumin,	3.0 [2.5–3.4]	2.9 [2.5–3.4]	3.0 [2.6–3.5]	30 (0.9)
Creatinine	1.64[1.00–2.75]	1.68[1.03–2.78]	1.56[0.92–2.68]	1
BUN	34 [22–55]	35 [23–57]	33 [21–52]	8 (0.2)
Bilirubin	0.8 [0.5–1.5]	0.9 [0.5–1.7]	0.7 [0.5–1.3]	3
pH	7.39[7.30–7.45]	7.39[7.32–7.46]	7.37[7.27–7.44]	90 (2.6)
$PaCO_2$	31.0[25.4–37.8]	30.0[25.0–36.4]	32.4[26.6–40.0]	90 (2.6)
PaO_2	79 [61–103]	80 [63–104]	77 [60–100]	91 (2.6)
Bicarbonate, mmol/L	19.2[15.2–23.2]	19.1[15.2–22.8]	19.9[15.3–23.6]	98 (2.8)
Lactate level, mmol/L	3.2 [1.8–5.9]	3.4 [1.9–5.9]	3.0 [1.7–5.7]	47 (1.3)
Procalcitonin, ng/mL	6.2 [0.8–34.8]	10.1 [1.5–47.1]	1.81[0.36–14.1]	1162 (33.2)
C-reactive protein, mg/dL	13.3 [5.1–21.9]	14.4 [6.5–23.4]	10.9 [3.5–19.5]	7 (0.2)
BNP, pg/mL	288 [117–848]	312 [128–915]	250 [96–741]	2210 (63.1)
Use of antibiotics before time zero	522 (15)	317 (14)	205 (16)	0

SOFA Sequential Organ Failure Assessment, *PLT* platelets, *CV* cardiovascular, *GCS* Glasgow coma scale, *ECOG* Eastern Cooperative Oncology Group, *BUN* blood urea nitrogen, *BNP* B-type natriuretic peptide, *ICU* Intensive Care Unit

*Missing data for proportions smaller than 0.1% are indicated only as numbers and not as percentages

higher neutrophilic fraction, lower albumin levels, higher levels of creatinine/blood urea nitrogen (BUN), lactate, CRP, procalcitonin, and B-type natriuretic peptide (BNP). Meanwhile, the culture-negative sepsis group had a lower arterial pH and higher $PaCO_2$ levels compared to the culture-positive sepsis group.

When patients were stratified by the presence or absence of septic shock, the differences in demographic and clinical characteristics between the culture-positive sepsis and culture-negative sepsis groups in sepsis patients without shock were similar to those observed among all sepsis patients (Table 2). However, in patients with septic shock, the differences in baseline severity between the two groups disappeared, and the previously higher SOFA scores for the P/F ratio in the culture-negative sepsis group were no longer evident in the culture-negative septic shock group. Notably, the culture-negative septic shock patients had a worse cardiovascular SOFA score than the culture-positive septic shock patients. While the distribution of sepsis foci remained similar in patients with septic shock, the difference in their frequencies narrowed. Culture-positive septic shock patients continued to exhibit higher body temperatures, higher inflammatory markers and worse underlying general conditions compared to the culture-negative septic shock patients. Meanwhile, prior antibiotic use immediately before time zero did not differ between the two groups across all these categories, including all sepsis patients, those without shock, and those with septic shock (Tables 1 and 2).

Difference in bundle compliance and *sepsis* management between the culture-positive *sepsis* and culture-negative *sepsis* groups

One-h, 3-h and 6-h bundle compliances were similar between the two groups (Table 3). There were missing cases for bundle components: 1.4% for lactate measurement, 18.3% for blood culture, 0.9% for antibiotics, 9.3% for fluid resuscitation. Culture-positive sepsis patients demonstrated earlier achievement for blood

Table 2 Baseline and clinical characteristics of sepsis patients referred to the ICU on the presence or absence of shock

Variables	Sepsis without shock (n = 2598)			Septic shock (n = 903)		
	Total (n = 2598)	Culture-positive sepsis (n = 1625)	Culture-negative sepsis (n = 973)	Total (n = 903)	Culture-positive septic shock (n = 588)	Culture-negative septic shock (n = 315)
Age, yrs	75 [65–82]	76 [65–82]	73 [64–81]	74 [63–81]	75 [64–81]	73 [61–79]
Sex, male, n (%)	1459 (56)	891 (55)	568 (58)	517 (57)	333 (47)	184 (58)
BMI, kg/m^2	21.6 [18.9–24.6]	21.8 [19.1–24.8]	21.4 [18.6–24.4]	21.7 [19.0–24.5]	21.6 [18.7–24.3]	21.9 [19.5–24.9]
Baseline SOFA score	6 [5–8]	6 [5–8]	6 [4–8]	9 [7–12]	9 [7–12]	9 [7–12]
	6.4 ± 2.7	6.6 ± 2.7	6.2 ± 2.6	9.28 ± 3.37	9.28 ± 3.37	9.27 ± 3.37
SOFA_PaO_2/FiO_2 ratio	2 [1, 2]	2 [1, 2]	2 [1, 2]	2 [1, 2]	2 [1, 2]	2 [1, 2]
	1.59 ± 1.05	1.50 ± 1.05	1.73 ± 1.04	1.78 ± 1.14	1.77 ± 1.15	1.81 ± 1.13
SOFA_PLT	0 [0–1]	0 [0–2]	0 [0–1]	1 [0–2]	1 [0–2]	0 [0–2]
	0.80 ± 1.11	0.90 ± 1.15	0.63 ± 1.01	0.99 ± 1.18	1.05 ± 1.19	0.88 ± 1.17
SOFA_Bilirubin	0 [0–1]	0 [0–1]	0 [0–1]	0 [0–1]	0 [0–2]	0 [0–1]
	0.57 ± 0.92	0.63 ± 0.97	0.46 ± 0.82	0.65 ± 0.96	0.75 ± 1.00	0.46 ± 0.83
SOFA_CV	1 [0–1]	1 [0–1]	1 [0–1]	3 [1–4]	3 [1–4]	3 [1–4]
	0.79 ± 0.86	0.80 ± 0.84	0.76 ± 0.90	2.60 ± 1.40	2.52 ± 1.41	2.76 ± 1.39
SOFA_GCS	1 [0–3]	1 [0–2]	1 [0–3]	2 [0–3]	2 [0–3]	2 [0–3]
	1.42 ± 1.32	1.41 ± 1.30	1.44 ± 1.35	1.78 ± 1.46	1.72 ± 1.44	1.90 ± 1.50
SOFA_Renal	1 [0–2]	1 [0–2]	1 [0–2]	1 [1, 2]	1 [1, 2]	1 [0–2]
	1.27 ± 1.28	1.30 ± 1.27	1.21 ± 1.29	1.48 ± 1.20	1.48 ± 1.18	1.47 ± 1.23
Clinical frailty score	6 [4–7]	6 [4–7]	5 [4–7]	6 [3–7]	6 [4–7]	5 [3–7]
	5.4 ± 2.0	5.5 ± 2.0	5.2 ± 2.0	5.26 ± 2.14	5.4 ± 2.1	4.9 ± 2.2
ECOG PS	2 [1–3]	3 [1–3]	2 [1–3]	2 [1–3]	3 [1–3]	2 [1–3]
	2.3 ± 1.3	2.3 ± 1.3	2.2 ± 1.3	2.2 ± 1.4	2.3 ± 1.4	2.0 ± 1.4
CCI	5 [4–7]	5 [4–7]	5 [4–7]	5 [4–7]	5 [4–7]	5 [3–7]
	5.4 ± 2.5	5.5 ± 2.5	5.3 ± 2.5	5.4 ± 2.5	5.5 ± 2.6	5.1 ± 2.4
Comorbidities						
Diabetes mellitus	996 (38.3)	638 (39.3)	358 (36.8)	356 (39.4)	242 (41.2)	114 (36.2)
Solid tumor malignancy	653 (25.1)	413 (25.4)	240 (24.7)	233 (25.8)	148 (25.2)	85(27.0)
Hematologic malignancy	74 (2.8)	45 (2.8)	29 (3.0)	46 (5.1)	29 (4.9)	17 (5.4)
Chronic neurologic disease	750 (28.9)	494 (30.4)	256 (26.3)	101 (26.6)	152 (25.9)	72(22.9)
Cardiovascular disease	686 (26.4)	428 (26.3)	258 (26.5)	211 (11.2)	151 (25.7)	60(19.0)
Chronic lung disease	368 (14.2)	194 (11.9)	174 (17.9)	114 (12.6)	68 (11.6)	46(14.6)
Chronic kidney disease	420 (16.2)	254 (15.6)	166 (17.1)	112 (12.4)	79 (13.4)	33(10.5)
Chronic liver disease	224 (8.6)	140 (8.6)	84 (8.6)	815 (8.7)	72 (12.2)	29 (9.2)
Immunocompromised	55 (2.1)	39 (2.4)	16 (1.6)	19 (2.1)	15 (2.6)	4 (1.3)
Type of infection						
Community-acquired	1761 (67.8)	1084 (66.7)	677 (69.6)	589 (65.2)	367 (62.4)	222 (70.5)
Hospital-acquired	204 (7.9)	153 (9.4)	51 (5.2)	62 (6.9)	56 (9.5)	6 (1.9)
Nursing hospital acquired	373 (14.4)	241 (14.8)	132 (13.6)	161 (17.8)	116 (19.7)	45 (14.3)
Nursing home-acquired	260 (10.0)	147 (9)	113 (11.6)	91 (10.1)	49 (8.3)	42 (13.3)
Source of sepsis						
Lung	1217 (46.8)	633 (39.0)	584 (60.0)	389 (43.1)	233 (39.6)	156 (49.5)
Intraabdominal	599 (23.1)	397 (24.4)	202 (20.8)	241 (26.7)	156 (26.5)	85 (27.0)

Table 2 (continued)

Variables	Sepsis without shock (n = 2598)			Septic shock (n = 903)		
	Total (n = 2598)	Culture-positive sepsis (n = 1625)	Culture-negative sepsis (n = 973)	Total (n = 903)	Culture-positive septic shock (n = 588)	Culture-negative septic shock (n = 315)
Urinary tract	497 (19.1)	429 (26.4)	68 (7.0)	156 (17.3)	127 (21.6)	29 (9.2)
Systemic infection wo 1° site	173 (6.7)	89 (5.5)	84 (8.6)	81 (9.0)	47 (8.0)	34 (10.8)
Skin or soft tissue	82 (3.2)	61 (3.8)	21 (2.2)	28 (3.1)	18 (3.1)	10 (3.2)
Nervous system	22 (0.8)	8 (0.5)	14 (1.4)	3 (0.3)	3 (0.5)	0 (0)
Catheter-related	8 (0.3)	8 (0.5)	0 (0.0)	5 (0.6)	4 (0.7)	1 (0.3)
Hemodynamics						
Mean arterial blood pressure, mmHg	69 [60–84]	69 [60–82]	70 [60–89]	59 [49–70]	60 [49–70]	57 [48–70]
Heart rate, beats/min	105 [88–120]	104 [88–120]	105 [88–122]	106 [88–125]	107 [89–124]	105 [84–126]
Respiratory rate, breaths/min	24 [22–26]	23 [20–26]	24 [22–28]	24 [20–27]	24 [20–28]	22 [20–26]
Body temperature, °C	37.1 [36.4–38.1]	37.2 [36.5–38.2]	36.9 [36.2–37.9]	36.8 [36.1–37.9]	37.0 [36.2–38.1]	36.7 [36.0–37.6]
Baseline lab findings						
WBC, 10^3/μL	11.7 [7.3–17.1]	11.7 [7.0–17.1]	11.7 [7.9–17.2]	12.3 [6.3–18.5]	12.4 [5.8–19.1]	12.3 [7.2–17.5]
Neutrophil, %	86.9 [78.5–91.6]	88.3 [80.3–92.3]	84.1 [76.1–90.0]	86.9 [78.5–92.0]	88.7 [80.4–93.0]	83.7 [74.8–89.8]
Hematocrit	33.0 [28.1–38.4]	32.9 [27.9–37.8]	33.2 [28.4–39.2]	32.4 [27.7–37.4]	32.3 [27.7–37.1]	32.8 [27.5–38.2]
Platelet,10^3/L	169 [102–251]	158 [94–237]	193 [122–270]	150 [83–237]	140 [80–221]	165 [92–270]
Albumin,	3.0 [2.6–3.5]	3.0 [2.5–3.4]	3.1 [2.6–3.6]	2.8 [2.4–3.2]	2.8 [2.4–3.2]	2.8 [2.4–3.3]
Creatinine	1.55 [0.94–2.70]	1.60 [0.98–2.74]	1.46 [0.88–2.59]	1.89 [1.20–2.90]	1.90 [1.21–2.89]	1.83 [1.13–2.97]
BUN	33 [22–55]	34 [22–58]	32 [20–51]	35 [23–55]	35 [23–55]	35 [23–55]
Bilirubin	0.8 [0.5–1.5]	0.9 [0.5–1.6]	0.7 [0.5–1.3]	0.9 [0.5–1.7]	1.0 [0.5–2.0]	0.8 [0.5–1.2]
pH	7.40 [7.32–7.46]	7.40 [7.33–7.46]	7.39 [7.29–7.45]	7.35 [7.24–7.43]	7.37 [7.28–7.44]	7.33 [7.18–7.41]
$PaCO_2$	31.5 [26.0 -38.0]	30.6 [25.3–36.5]	33.0 [27.0–40.0]	29.8 [24.0–37.5]	29.0 [24.0–36.2]	31.0 [25.0–39.7]
PaO_2	79 [61–102]	81 [64–104]	77 [58–97]	79 [62–108]	80 [62–105]	78 [62–109]
Bicarbonate, mmol/L	20.1 [16.0–23.8]	19.6 [15.8–23.4]	20.7 [16.5–24.4]	17.2 [12.9–20.8]	17.6 [13.6–20.9]	16.9 [12.3–20.8]
Lactate level, mmol/L	2.6 [1.5–4.9]	2.8 [1.6–5.1]	2.4 [1.4–4.7]	5.0 [3.3–7.9]	5.1 [3.3–7.8]	5.0 [3.3–8.5]
Procalcitonin, ng/mL	4.5 [0.6–26.6]	9.1 [1.4–41.5]	1.2 [0.29–7.6]	11.04 [1.57–54.68]	14.80 [2.28–59.86]	7.00 [0.94–36.04]
C-reactive protein, mg/dL	13.4 [4.8–22.2]	14.8 [6.6–23.6]	10.1 [3.2–19.5]	13.1 [5.8–21.3]	13.6 [6.2–22.9]	12.0 [5.0–19.4]
BNP, pg/mL	288 [116–835]	308 [127–873]	252 [93–743]	293 [126–935]	338 [134–1049]	244 [103–755]
Use of antibiotics before time zero	370 (14.2)	223 (13.7)	147 (15.1)	152 (16.8)	94 (16.0)	58 (18.4)

BMI Body mass index, *SOFA* Sequential Organ Failure Assessment, *PLT* platelets, *CV* cardiovascular, *GCS* Glasgow coma scale, *ECOG PS* Eastern Cooperative Oncology Group performance status, *CCI* Charlson comorbidity index, *BUN* blood urea nitrogen, *BNP* B-type natriuretic peptide, *ICU* Intensive Care Unit

cultures and administration of empirical antibiotics, as well as higher achievement rates for rapid fluid resuscitation for the first 6 h, whereas the culture-negative sepsis patients had a higher vasopressor application rate within the first hour with lower pre-ICU fluid input in emergency department. We compared compliance between subgroups based on the presence or absence of shock (Supplementary Table 1). A similar trend observed in all sepsis patients was also seen in those without shock. However, in patients with septic shock, these difference in bundle elements between the two groups disappeared. Nonetheless, the earlier use of vasopressors in culture-negative sepsis patients was notably more pronounced, along with less pre-ICU fluid administration, although this difference was not statistically significant.

Table 3 Sepsis bundle compliance and sepsis management (n = 3,501)

Variables	Culture-positive sepsis (n = 2213)	Culture-negative sepsis (n = 1288)	P-value
Bundle compliance			
1-h	164 (9.6)	92 (10.8)	0.330
3-h	962 (56.2)	456 (53.6)	0.205
6-h	1459 (85.3)	715 (84.0)	0.405
Bundle elements			
Lactate			
1-h	1923 (88.2)	1149 (90.3)	0.064
3-h	2122 (97.3)	1240 (97.4)	0.904
6-h	2151 (98.7)	1261 (99.1)	0.310
Blood culture			
1-h	1207 (64.1)	594 (60.9)	0.089
3-h	1693 (89.9)	841 (86.2)	0.003
6-h	1821 (96.7)	926 (94.9)	0.017
Antibiotics			
1-h	397 (18.0)	227 (17.9)	0.912
3-h	1502 (68.2)	823 (64.9)	0.041
6-h	2014 (91.5)	1138 (89.7)	0.072
Fluid resuscitation			
1-h	1107 (82.9)	573 (83.3)	0.836
3-h	1265 (94.8)	649 (94.3)	0.688
6-h	1313 (98.4)	667 (96.9)	0.038
Vasopressor			
1-h	534 (31.1)	327 (35.9)	0.012
3-h	1136 (66.1)	621 (68.2)	0.281
6-h	1466 (85.3)	781 (85.7)	0.757
Sepsis management			
Pre-ICU input (mL/kg)	35.1 [21.2–53.5]	31.4 [16.9–48.3]	< 0.001
Appropriate empirical antibiotics within 24 h	1859 (84.1)	1253 (98.0)	< 0.001
Source control	427 (19.3)	130 (10.1)	< 0.001
Steroid use for sepsis	554 (25.0)	275 (21.4)	0.013
Time to management			
Time to obtain blood cultures (min)	38 [20–90]	43 [22–105]	0.007
Time to broad-spectrum antibiotics (min)	128 [73–206]	137 [75–225]	0.041
Time to begin rapid fluid administration (min) n = 2047 m = 1454	16 [8–40]	15.5 [6–38]	0.313
Time to apply vasopressor (min)	112 [48–247]	101 [40–233]	0.010
Time to source control (min)	614 [335–1448]	715 [291–1974]	0.738
Time to administer steroid (min)	389 [191–1053]	456 [164–1175]	0.786

Culture-negative sepsis patients were more likely to receive appropriate antibiotics within 24 h, but it took significantly longer to administer antibiotics compared to the culture-positive sepsis group (Table 3). The same pattern was identified in patients with septic shock (Supplementary Table 1). Culture-positive sepsis patients had a higher rate of source control and more frequent use of adjunctive steroids. While source control showed consistent results regardless of shock status, the frequency of steroid use was not significantly higher in culture-positive patients without shock compared to the culture-negative patients.

ICU course

Upon ICU admission, the culture-negative sepsis group exhibited a lower SOFA score compared with the culture-positive sepsis group, and this discrepancy persisted until ICU day 3. Notably, significant differences were observed in each component of the SOFA score between the two groups. The culture-positive sepsis group exhibited

higher scores for cardiovascular and hepatic failure, as well as coagulopathy, while the culture-negative sepsis group demonstrated a higher score for respiratory failure. Regarding early interventions in the ICU, the use of vasopressors and adjunctive corticosteroids were common in the culture-positive sepsis group, while the invasive mechanical ventilation was more prevalent in the culture-negative sepsis group (Supplementary Table 2).

Hospital outcomes

Among all patients with sepsis referred to the ICU, in-hospital mortality did not significantly differ between the two groups (31.6% vs. 34.9%, p = 0.073, culture-positive sepsis vs. culture-negative sepsis) (Table 4). However, among patients with septic shock, culture-negative patients had worse outcomes compared to culture-positive patients (in-hospital mortality, 37.6% vs. 45.1%, p = 0.029, culture-positive septic shock vs. culture-negative septic shock). A multivariate analysis for patients with septic shock revealed that culture-negativity was an independent prognostic factor for in-hospital mortality (OR 1.462, 95% CI [1.060–2.017], p = 0.021) (Table 5 and Supplementary Table 3).

Discussion

This study investigated the disparity between culture-positive and culture-negative sepsis, specifically focusing on 3501 patients referred to ICUs from the emergency department out of a cohort of 11,981. To our knowledge, it stands as the largest cohort study exploring the significance of culture negativity in sepsis patients, employing the Sepsis-3 definition as the diagnostic criterion. In all patients, culture-negative sepsis showed similar mortality to culture-positive sepsis despite lower severity of

Table 4 Clinical outcomes of patients with culture-positive sepsis and culture-negative sepsis

Variables	Culture-positive (n = 2213)	Culture-negative (n = 1288)	P-value
All patients, n = 3501			
Hospital outcome			
Dead	706 (31.6)	449 (34.9)	0.073
Alive	1507 (68.1)	839 (65.1)	
Discharge to home	809 (53.7)	494 (58.9)	0.015
Transferred to other facilities	698 (46.3)	345 (41.1)	
Step-down	691 (99.0)	340 (98.6)	0.525
Step-up	7 (1.0)	5 (1.4)	
ICU outcome			
Dead	526 (23.8)	325 (25.2)	0.330
Patients with sepsis without shock, n = 2598	n = 1625	n = 973	
Hospital outcome			
Dead	485 (29.8)	307 (31.6)	0.361
Alive	1140 (70.2)	666 (68.4)	
Discharge to home	624 (54.7)	393 (59.0)	0.077
Transferred to other facilities	516 (45.3)	273 (41.0)	
Step-down	510 (98.8)	269 (98.5)	0.718
Step-up	6 (1.2)	4 (1.5)	
ICU outcome			
Dead	342 (21.0)	209 (21.5)	0.793
Patients with septic shock, n = 903	n = 588	n = 315	
Hospital outcome			
Dead	221 (37.6)	142 (45.1)	0.029
Alive	367 (62.4)	173 (54.9)	
Discharge to home	185 (50.4)	101 (58.4)	0.083
Transferred to other facilities	182 (49.6)	72 (41.6)	
Step-down	181 (99.5)	71 (98.6)	0.495
Step-up	1 (0.5)	1 (1.4)	
ICU outcome			
Dead	184 (31.3)	116 (36.8)	0.092

Table 5 Predictors for hospital mortality for patients with septic shock referred to the ICU

Variables	OR	95% CI	P-value
Inappropriate empirical antibiotics	2.179	1.350–3.517	0.001
Culture-negativity	1.462	1.060–2.017	0.021
Adjunctive corticosteroids	1.455	1.057–2.002	0.022
Baseline lactate level	1.133	1.088–1.181	< 0.001
Baseline SOFA score	1.124	1.069–1.183	< 0.001
Clinical frailty score	1.101	1.019–1.190	0.015
Charlson comorbidity index	1.079	1.008–1.157	0.030
Source control	0.604	0.382–0.955	0.031
Diabetes (organ damage or uncontrolled)	0.518	0.374–0.716	< 0.001
Urinary tract sepsis	0.375	0.228–0.618	< 0.001

Multivariate analysis was conducted with significant univariate variables such as age, sex, Charlson comorbidity index, clinical frailty score, comorbidities (diabetes and chronic lung disease), site of infection (lung and urinary tract), baseline SOFA score, baseline lactate level, culture-negativity, treatments (inappropriate empirical antibiotics, application of vasopressor within 1 h after time zero, source control and adjunctive corticosteroids)

SOFA Sequential Organ Failure Assessment

disease. When confined to septic shock, culture-negative sepsis showed an obviously higher mortality rate than culture-positive sepsis. Interestingly, the appropriateness of empirical antibiotics was paradoxically higher in the culture-negative sepsis group than in the culture-positive sepsis group. In a multiple logistic regression analysis, culture negativity was an independent predictor of in-hospital mortality in these patients.

Our results underscored the clinical distinctiveness of culture-negative sepsis compared with culture-positive sepsis. Culture-negative sepsis patients presented with milder disease severity at the time of detection, evidenced by fewer organ failures, better maintenance of initial blood pressure compared with culture-positive sepsis patients. Additionally, culture-negative sepsis patients displayed less pronounced initial lactate elevation and inflammatory markers than those in the culture-positive sepsis group. These findings align with most previous studies [2, 6, 13]. However, we did not find any significant difference between the two groups in antibiotic use before the onset of sepsis, which had been identified as the main reason for the difference in the previous study [1]. The contrasting profiles between culture-positive sepsis and culture-negative sepsis can be partly attributed to the predominant site of infection. Although both groups most commonly presented with pulmonary infections, a higher proportion of culture-negative patients had pulmonary infections, while the incidence of UTIs was lower (8%). In contrast, culture-positive patients had a relatively higher proportion of UTIs (25%). These differences in the primary infection site are further reflected in the higher SOFA score for the P/F ratio component in the culture-negative sepsis group, whereas the more pronounced inflammatory markers and hemodynamic instability in the culture-positive sepsis group.

Despite culture-positive patients being older, having worse baseline underlying conditions, as indicated by higher clinical frailty score or Charlson comorbidity index, and higher baseline severity compared to culture-negative patients, there was no significant difference in hospital mortality between the two groups. Several factors may contribute to this finding. First, culture-negative sepsis patients predominantly suffered from respiratory dysfunction, while the culture-positive sepsis group primarily experienced hepatic dysfunction and coagulopathy. This suggests that a higher incidence of respiratory failure and the resulting increased need for invasive mechanical ventilation in the culture-negative group may have acted as a poor prognostic factor. Second, in the management of sepsis, the culture-negative sepsis group received blood cultures and empirical antibiotic administration less promptly than the culture-positive sepsis group, which may have influenced the clinical outcome. The delayed interventions in culture-negative patients may have occurred because their inflammatory markers or febrile illness were less prominent compared to culture-positive patients. Third, the culture-negative sepsis group received less initial fluid resuscitation and was administered vasopressor earlier compared to the culture-positive sepsis group. This disadvantage already existed at the emergency department where the culture-negative sepsis group received a smaller volume of fluids until ICU admission than the culture-positive sepsis group. This difference likely played a significant role in the outcomes of initial sepsis management, as insufficient early fluid resuscitation or the early use of vasopressors can be associated with a poor prognosis in septic patients [11, 14–16]. Additionally, compared to culture-positive patients, culture-negative patients were less likely to undergo source control, which could impact survival of sepsis patients [17–20]. UTI is known to be a good prognostic factor in sepsis [21, 22]. The lower proportion of UTI as cause in the culture-negative sepsis group as compared with the culture-positive sepsis group could have been another disadvantage in survival.

Furthermore, we found a difference in outcomes between the two groups of patients with septic shock. Culture-negative septic shock patients had a significantly higher mortality rate compared to culture-positive septic shock patients. Interestingly, the differences in clinical characteristics observed in the whole sepsis group disappeared in these sicker patients. Between the culture-positive septic shock and culture-negative septic shock groups, there were found no differences in severity

scores, baseline hemodynamic parameters, or the frequency of respiratory failure. In terms of sepsis management, culture-negative septic shock patients received more vasopressors and less pre-ICU fluid administration than culture-positive septic shock patients. Data including our previous study showed that early administration of vasopressors was associated with poorer prognosis in patients with septic shock [11, 14]. In the culture-negative septic shock group, source control was also less performed. Adjunctive steroids were used less frequently in culture-negative septic shock patients. In view that steroid use was a poor prognostic indicator in the logistic regression analysis, it is difficult to determine whether less steroid use in this group was a cause or a consequence.

Culture-negativity was an independent prognostic factor for hospital mortality in patients with septic shock. The appropriateness of empirical antibiotics appeared to be higher in the culture-negative septic shock group than in the culture-positive septic shock group. Logistic regression analysis showed that inappropriate antibiotic use was associated with worse outcomes, which was more pronounced in patients with septic shock, as shown in other studies [23, 24]. Interestingly enough, culture-negative septic shock patients had worse outcomes despite receiving 'appropriate' empirical antibiotics more frequently than culture-positive septic shock patients. These contradictory results suggest that antibiotics considered appropriate for culture-positive patients may not be valid for culture-negative patients when the disease is severe enough. Additionally, culture-negativity was an independent prognostic factor in septic shock patients. These findings raise concerns about current antibiotic practices in sepsis, including the initial empirical choice and antibiotic de-escalation (ADE). While the precise approach to ADE in culture-negative cases remains unsettled, existing guidelines recommend de-escalation of antibiotics if the patient shows clinical improvement [25–28]. As the current guidelines on empirical antibiotics in sepsis do not guarantee the true appropriateness of antibiotics in culture-negative septic shock, the same caution holds true for changing antibiotics during the management of these patients. Our results support a study by Kethireddy et al. [4], which underscored the need to reevaluate antibiotic strategies in culture-negative patients, particularly those with shock.

The strength of our study is that we used a nationwide multicenter prospective cohort, whereas existing studies are mainly single-center studies [1, 2, 5, 6, 13] or retrospective cohort studies [1, 4–6, 13]. Second, we collected major clinical data at the time of initial management of sepsis. The execution time for each bundle element was collected, and bundle compliance for each element was assessed at key time points (1-h, 3-h, and 6-h). These strengths enabled practical analysis related to the real-world sepsis management, particularly in identifying the differences between culture-positive sepsis and culture-negative sepsis, such as fluid resuscitation or vasopressor use.

Our study has several limitations. First, it excluded sepsis caused by non-bacterial pathogens or confirmed by non-culture methods. Thus, caution is needed when interpreting our results beyond the scope of bacterial sepsis. Second, regarding the classification into culture-positive or culture-negative, some cases may have been classified as culture-negative due to insufficient testing. Additionally, technical issues may have affected the bacterial culture outcomes. For these reasons, the classification of culture-negative sepsis may not fully reflect the actual condition. However, as patients in our cohort underwent a broad range of cultural and serologic tests for pathogenic microorganisms, it seems unlikely that the culture-negative group was significantly contaminated by hidden non-bacterial pathogens. In this context, the authors believe that culture-negative sepsis, as defined in our study, reflects real-world clinical practice. Third, there were significant differences in baseline demographic characteristics, illness severity, and treatment approaches between the culture-positive sepsis and culture-negative sepsis groups. Therefore, outcome comparisons between the two groups need to be interpreted with caution. Fourth, recruiting sepsis patients from tertiary and university-based teaching hospitals may limit the generalizability of our results to other clinical settings, such as smaller community hospitals.

In conclusion, culture-negativity may be a poor prognostic factor in sepsis. Particularly in patients with septic shock, culture-negativity was associated with increased mortality, despite the paradoxically higher appropriateness of empirical antibiotic therapy than culture-positive patients. These findings suggest that the current criteria for determining the appropriateness of empirical antibiotics may not be valid for culture-negative sepsis.

Abbreviations

ADE	Antibiotic de-escalation
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CRP	C-reactive protein
ECOG	Eastern Cooperative Oncology Group
ICU	Intensive care unit
IQR	Interquartile range
MDR	Multidrug-resistant
PCR	Polymerase chain reaction
P/F	PaO_2/FiO_2
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment
UTI	Urinary tract infection

Supplementary Information

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Supplementary Material 1

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Declarations

Ethics approval and consent to participate
The study protocol was approved by the Institutional Review Board of each participating hospital, including Inje University Sanggye Paik Hospital (Approval No. 2018-08-014-013), and the requirement for obtaining patient informed consent was waived because of the observational nature of the study. Additionally, the patient's information was anonymized and de-identified prior to analysis.

Consent for publication
Not applicable.

Competing Interests
The authors declare that they have no competing interests.

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